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## **Unrecognized pediatric adult-type tuberculosis puts school contacts at risk**

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; Berger, Christoph ; Nadal, David

**Abstract:** Adolescents with an immigrant background who are from tuberculosis high-incidence regions were at highest risk to develop adult-type tuberculosis disease in a low-incidence region during a 20-year period. If diagnosis and treatment were delayed up to 6 months, latent tuberculosis infection was detected in almost half of the affected individuals' school contacts.

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unavailable. Health care providers in our region must consider Buruli ulcer in any patient with a suggestive lesion and either refer to a tertiary care facility for diagnosis or initiate therapy accordingly.

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## UNRECOGNIZED PEDIATRIC ADULT-TYPE TUBERCULOSIS PUTS SCHOOL CONTACTS AT RISK

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**Abstract:** Adolescents with an immigrant background who are from tuberculosis high-incidence regions were at highest risk to develop adult-type tuberculosis disease in a low-incidence region during a 20-year period. If diagnosis and treatment were delayed up to 6 months, latent tuberculosis infection was detected in almost half of the affected individuals' school contacts.

**Key Words:** tuberculosis, child, cavity disease, adult-type, resistance

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The age-related risk of disease following *Mycobacterium tuberculosis* infection is greatest in children <4 years, reaches a nadir in those between 5 and 10 years and increases rapidly during adolescence.<sup>1</sup> In infants and toddlers, extrapulmonary disease including tuberculous meningitis or miliary tuberculosis is common and in adolescence a shift of pathology toward adult-type disease (ATD) is observed.<sup>2,3</sup>

Tissue destruction and lung cavitation hallmark ATD that may develop 1–3 years after primary *M. tuberculosis* infection.<sup>4</sup> Unrecognized ATD puts household members or school contacts at risk for tuberculosis.<sup>5</sup> Rare reports on pediatric ATD in the chemotherapy era exclusively originate from regions with high tuberculosis incidence.<sup>6–9</sup> We aimed at reviewing pediatric ATD patients in a low tuberculosis incidence region to define the individuals at risk and to assess their transmission potential.

## PATIENTS AND METHODS

### Patients

A diagnosis code inquiry served to gather all patients <16 years hospitalized because of tuberculosis at the University Children's Hospital of Zurich from 1990 through 2011. This period was chosen because of electronic availability of diagnosis codes. Demographic data were extracted by chart review and information on clinical, laboratory and imaging findings, diagnosis establishment, treatment and course was retrieved for ATD patients. ATD was defined as the presence of a pulmonary cavity in imaging<sup>4</sup> and detection of *M. tuberculosis* in sputum, gastric lavage (GL) or bronchoalveolar lavage (BAL). The institutional review board approved the study.

### Contact Investigations

The staff of the lung league prospectively investigated family members and close contacts (> 8 hours cumulative exposure), both hereafter referred to as household contacts, plus school contacts (classmates and teachers) of ATD patients based on Swiss law ([http://www.admin.ch/ch/d/sr/818\\_101/a16.html](http://www.admin.ch/ch/d/sr/818_101/a16.html)). In clinically healthy individuals, investigations included a tuberculin skin test (TST) and, if induration was ≥5 mm, a chest X-ray, or if induration was < 5 mm, a second TST 8 weeks later. Individuals exposed to the source cases and showing positive TST (induration ≥ 5 mm) in the absence of physical findings of disease were regarded to have latent tuberculous infection (LTBI) if chest X-ray was normal or revealed evidence of healed infection. Data for this work were obtained from the records of the lung league.

### Statistics

Independent t-test was performed for statistical calculations regarding age and exact Fisher's test for those regarding sex

**TABLE 1.** Synopsis of Demographics, Clinical Characteristics, Treatment and Course in 5 Pediatric Patients With Adult-type Tuberculosis

Case	Age (years), Sex	Country of Origin	Time Family Living in CH	Signs and Symptoms at First Presentation (Duration)/time First Presentation to Physician Till Diagnosis	CRP (mg/L)/BSR (mm/h)	TST (Induration mm)	AFB+ in Microscopy	Antituberculous Treatment (Total Duration)	Last Follow Up After Treatment (Months)	Lung Function	Contact Investigation	
											In Household n LTBI + / n Tested	In School n LTBI + / n Tested
1	16, M	Haiti	3 years	Cough (8 weeks); night sweats, headache (2 weeks) / 9 weeks	38/7	26	Sputum	Ciprofloxacin, RMP, PZA, EMB (6 months)	6	Normal	n.a.	n.a.
2	12, F	Pakistan	3 years	Cough, night sweats, fever, 8.6% weight loss, vomiting fatigue, abdominal pain, diarrhea (3 weeks) / < 1 week	48/ND	0	Gastric lavage	INH, RMP, PZA (9 months)	24	Obstructive ventilation disorder: PEF 63%	n.a.	n.a.
3	12, F	Croatia	12 years	Cough (2 weeks), night sweats, fever, 20% weight loss, fatigue, vomiting, loss of appetite/6.5 months	87/93	18	BAL	INH, RMP, PZA, EMB (6 months)	28	Obstructive ventilation disorder: FVC 87%, FEV <sub>1</sub> 71%	Children: 3/12 (25%)	Children: 19/40 (48%)
4	14, M	Kosovo	8 years	Cough (3 weeks); 16% weight loss (3 months); chest pain, palpitations, dyspnea during exercise/2.5 months	128/73	0	Sputum	INH, RMP, PZA (9 months)	48	Restrictive and obstructive ventilation disorder: FVC 66%, FEV <sub>1</sub> 60%	Adults: 4/4 (100%) Children: 5/5 (100%)	Adults: 3/15 (20%) Children: 3/21 (14%)
5	13, F	Tibet	10 months	Cough, fever, fatigue, loss of appetite (10 days) / 1 week	16/49	17	Sputum	INH, RMP, PZA, EMB (6 months)	18	Normal	Adults: 1/2 (50%) Children: 4/6 (60%)	Adults: 1/3 (33%) Children: 1/20 (5%)
											Adults: 0/4 (0%) Adults: 0/2 (0%)	

AFB, acid-fast bacilli; BSR, blood sedimentation rate; CH, Switzerland; CRP, C-reactive protein; LTBI +, latent tuberculous infection positive; M, male; F, female; RMP, rifampin; PZA, pyrazinamide; EMB, ethambutol; INH, isoniazid; n.a., not available; PEF, peak expiratory flow; ND, not done; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 second.

and immigrant background using IBM SPSS Statistics 21.0, 2012 (Armonk, NY).  $P < 0.05$  were regarded as statistically significant.

## RESULTS

### Patient Demographics

A total of 45 patients were hospitalized because of tuberculosis in our hospital within 1990–2011: 26 with pulmonary tuberculosis including 5 with ATD plus 19 with extrapulmonary tuberculosis including 2 with miliary tuberculosis and 5 with meningitis. Patients with ATD (median 13.2 years, range 12.4–16.2; cases 1–5, Table 1) were older than patients with non-ATD pulmonary tuberculosis (6.9, 0.1–19.4,  $P = 0.044$ ) or extrapulmonary tuberculosis (1.8, 0.1–11.1,  $P < 0.05$ ). The proportions with immigrant background were 100% for ATD (Table 1) and 72.5% for non-ATD tuberculosis or extrapulmonary tuberculosis ( $P = 0.31$ ). There was no significant difference regarding sex distribution between ATD patients versus non-ATD pulmonary or extrapulmonary tuberculosis patients ( $P = 0.63$ ). Three non-ATD pulmonary tuberculosis patients had congenital immunodeficiency (chronic granulomatous disease, Wiskott-Aldrich syndrome or Nezelof syndrome) and 1 was HIV positive.

ATD case 2 travelled last to Pakistan 1 year before diagnosis, case 3 to Croatia 10 months before first symptoms and case 4 to Kosovo 8 and 3 years before diagnosis, respectively, and had often visits from Kosovo until diagnosis. Case 5 immigrated from Tibet 10 months before diagnosis (Table 1).

### Clinical Characteristics of ATD Patients

Cough, fever, night sweats, fatigue or weight loss were the main symptoms. The presenting symptoms at first physician consultation had lasted  $< 2$  months. Time from consultation to diagnosis was between  $< 1$  week and 6.5 months (Table 1). TST was positive in 3 patients (Table 1). HIV serology was not done in case 2 and negative in the other cases.

### Microbiological Findings

Acid-fast bacilli were detected by microscopy in sputum, BAL or GL in all ATD patients. *M. tuberculosis* grew in cultures from sputum ( $n = 4$ ) or if not available from BAL ( $n = 1$ ). The isolate of case 1 was isoniazid resistant.

### Treatment and Course in ATD patients

Two patients received isoniazid, rifampin and pyrazinamide for 2 months followed by isoniazid and rifampin for 7 months. Two patients received isoniazid, rifampin, pyrazinamide and ethambutol for 2 months followed by isoniazid and rifampin for 4 months. One patient received isoniazid that was replaced by ciprofloxacin after 3 weeks, rifampin, pyrazinamide and ethambutol for 2 months, followed by ciprofloxacin and rifampin for 4 months because of isoniazid resistance.

Signs and symptoms improved during treatment in all 5 patients. They were discharged in good general conditions after a mean hospitalization of 23.6 days (range, 14–28). Cases 1 and 5 recovered completely. Cases 2 and 3 showed obstructive ventilation 24 and 28 months, respectively, after ending treatment. Case 4 showed restrictive and obstructive ventilation and growth retardation 4 years after ending treatment (Table 1). Chest X-rays at the end of treatment showed residual changes in all patients.

### Contact Investigations

Information on contact investigations was not available for cases 1 and 2. For case 3, LTBI was diagnosed in 3 of 12 pediatric and 4 of 4 adult household contacts, 19 of 40 classmates and in 3

of 15 teachers. For case 4, LTBI was diagnosed in all 5 pediatric and 1 of 2 adult household contacts and in 3 of 21 classmates and 1 of 3 teachers. For case 5, LTBI was diagnosed in 4 of 6 pediatric and none of 4 adult household contacts, and in 1 of 20 classmates and none of 2 teachers. Isoniazid prophylaxis was recommended to all pediatric contacts with LTBI, but the proportion of those taking isoniazid is not known. No tuberculosis disease was diagnosed.

## DISCUSSION

We delineated the characteristics of ATD patients and assessed their transmission potential in a low tuberculosis incidence region. We found that ATD patients were older than other pediatric hospitalized tuberculosis patients, had invariably immigrant family background, were generally successfully treated, although minor respiratory impairment was possible, and many of the close contacts had LTBI.

One-tenth of the hospitalized pediatric tuberculosis patients showed ATD, and ATD patients were adolescents. Swiss law demands reporting and isolation of tuberculosis patients (practically always in hospital), as long as they are highly contagious, that is, they have detectable acid-fast bacilli in sputum or have not received effective antituberculous treatment for at least 2 weeks. ATD patients must be regarded as highly contagious.<sup>3</sup> Thus, their outpatient treatment in the Swiss community is unlikely. Other pediatric tuberculosis patients are rather hospitalized only when severe disease manifests. Thus, the proportion of ATD patients among all pediatric tuberculosis patients in Switzerland is likely to be less than the approximate 10% seen in this study. In tuberculosis high-incidence regions, the proportion of ATD patients among pediatric tuberculosis patients was 12.8%.<sup>8</sup> The age disparity among pediatric patients with distinct tuberculosis disease manifestations in our hospitalized patients and Switzerland (Data, Supplemental Digital Content 1, <http://links.lww.com/INF/B703>) matches that reported from high-incidence regions.<sup>10</sup>

Four ATD patients had immigrated to Switzerland from high-incidence regions 10 months to 7 years before diagnosis of ATD. Case 3 was born in Switzerland and her parents were immigrants from a high-incidence country. Data from the Swiss Federal Office of Public Health for 1996–2011 show that 90.3% and 92.1% of reported tuberculosis cases in the age groups 10–14 and 15–19 years, respectively, have an immigrant background (Data, Supplemental Digital Content 1, <http://links.lww.com/INF/B703>) and thus a similar frequency. The natural history of tuberculosis disease indicates that adolescents are at high risk to develop ATD 1–3 years after primary infection or as a reactivation disease.<sup>4</sup>

None of our ATD patients was critically ill. All of them showed fast recovery after the start of efficacious drug therapy and limited respiratory sequelae. Similar data were reported from South Africa<sup>6,11</sup> and Korea.<sup>7</sup> These observations have at least 2 implications. First, ATD patients may escape diagnosis while highly contagious, because their illness may not be impressive enough for an urgent work-up. This puts household and school contacts at significant risk for infection with *M. tuberculosis* that may even be drug resistant as shown here and elsewhere.<sup>6</sup> Notably, diagnosis in our case 3 was delayed over half a year and almost half of her school contacts had LTBI. Second, antibiogram-guided antituberculosis treatment leads to rapid reduction of contagiousness and cures ATD, albeit some impairment of lung function is possible as seen in our patients.

Our work has the limitations of a retrospective study that may miss data that are no longer retrievable and may suffer from information bias. The low number of patients with ATD may be regarded as limitation but this seems to be the reality of the situation in an industrialized country.



Adolescents with immigrant background from regions with higher tuberculosis incidence than in Switzerland are more likely to present with ATD in low-incidence regions. Antituberculosis drugs resolve ATD although respiratory sequelae are possible. Most importantly, ATD patients may escape recognition and—if treatment is delayed—significant transmission of *M. tuberculosis* to close contacts may take place due to the high contagiousness.

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## DIFFERENT PENETRANCE OF DISSEMINATED INFECTIONS CAUSED BY NONTUBERCULOUS MYCOBACTERIA IN MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASE ASSOCIATED WITH A NOVEL MUTATION

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**Abstract:** Deficiency in the interleukin12/INFgamma pathway is a genetic condition that predisposes to some infections, including nontuberculous mycobacteria infection and extraintestinal salmonellosis. We report 2 cases in sisters who were diagnosed with a genetic defect caused by a new mutation in Interleukin-12 receptor  $\beta 1$  chain (IL12R $\beta 1$ ) leading to different clinical presentations and responses to therapy.

**Key Words:** immunodeficiency, mycobacterial infection, genetic mutation, interleukin, interferon

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**M**endelian susceptibility to mycobacterial disease (MSMD) is a rare genetic disorder that carries an increased predisposition to suffer nontuberculous mycobacteria (NTM), *Bacille Calmette-Guérin* or *Salmonella spp.* infections in apparently healthy individuals.<sup>1</sup> Interleukin-12  $\beta 1$  receptor deficiency (IL12R $\beta 1$ ) was the first MSMD defect reported and to date it is the most prevalent.<sup>2,3</sup>

*Mycobacterium genavense's* ability to cause disease in humans is extremely rare and probably underestimated due to its slow and fastidious growing characteristics. NTM infections have been classically described in HIV-infected patients.<sup>4</sup> Recently, advances in antiretroviral therapy have been able to reduce the incidence of opportunistic infections like NTM.<sup>5</sup> However, new cases are emerging associated with newly diagnosed primary immunodeficiencies.<sup>4</sup> On the other hand, other NTM such as *Mycobacterium fortuitum* have been associated with skin infections secondary to trauma or surgical procedures, traumatic ulcers, corneal keratitis, lung disease, lymphadenitis or osteomyelitis.<sup>6</sup>

## CASE REPORTS

The first patient, who was a 5-year-old Caucasian female born in Spain to consanguineous parents (first cousins), was admitted to Torrecardenas Hospital (Almeria, Spain) in February 2010 with diarrhoea, bloating, fever mostly in the evenings and weight loss during the previous 9 months. Physical examination revealed severe abdominal distension although nontender to palpation, splenomegaly and moderate malnutrition. Serological tests for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, Epstein-Barr virus, *Coxiella burnetii*, Cytomegalovirus, toxoplasma, viral hepatitis, HIV and tuberculosis skin test were all negative. Gastrointestinal endoscopy was performed revealing chronic granulomatous colitis with abundant acid-fast bacilli that did not grow in standard culture conditions (Lowenstein-Jensen and BACT/Alert MP media). The bacilli was identified as *M. genavense* directly from the specimen by amplification and sequencing of 366 bp of the *hsp65* gene, obtaining a 100% alignment with the *M. genavense* sequences AJ310235, AF547837 and AB292585 deposited in GenBank. Given these findings, the patient was started on treatment with rifampicin, clarithromycin, ethambutol and levofloxacin (these last 2 antibiotics were replaced by amikacin and ciprofloxacin due to persistent infection after 10 months of treatment). Six months later the patient was readmitted on 2 occasions after developing *Salmonella enteritidis* sepsis confirmed by blood and stool cultures. Peripheral blood mononuclear cells (PBMCs) obtained from the patient were cultured in vitro with Phytohemagglutinin (PHA; GIBCO#cat: 10576-015) at 1.5% for 72 hours. Supernatants were collected to measure cytokine levels and lymphocytes were stained with CD212-PE, CD3 PercP and CD25-FITC and analyzed by flow cytometry. CD212 (IL12R $\beta 1$ ) expression was absent in the patient. Sequencing analysis of *IL12R $\beta 1$*  gene showed a novel homozygous deletion (g.1019\_1020delAC) affecting codon His-339 in exon 9 and resulting in a frame shift mutation, not previously described. Given the definitive